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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,217	11/18/2005	Masaomi Tajimi	RCK-40	2662

35969 7590 04/19/2007

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
O DELL, DAVID K	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,217	TAJIMI ET AL.	
	Examiner	Art Unit	
	David K. O'Dell, Ph.D.	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 19-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7 and 19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3 June 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 7, 19-26 are pending in the current application.

2. This is application is a national stage of PCT/EP2003/013452, filed November 28, 2003, which claims the priority of European Union Application EP 02027528.5, filed December 9, 2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3, 5, 7, 25, 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3, 5, 7 recite substituents that have no definite meaning including "aminocarbonyl", "alkoxycarbonyl" these terms have no meaning. The term "carbonyl" is for a functional group however carbonyl can be a portion of an amide, acid, ester, aldehyde, ketone, metal carbonyl, etc. and can encompass compounds of an indefinite scope and as written has a dangling valance (See Ex Parte Diamond (POBA 1959) 123 USPQ 167). These claims also recite mono- di- & tri-halogen. The examiner is unsure what this means. Iodine may exist as triiodide in solution, but not as a substituent attached to carbon. Halogens in their pure state are diatomic, the examiner knows of no substituents that can be dihalogen (implying an impossible situation with two bonds to chlorine or fluorine). When an optional substituent is "C_{1-6}-alkylamino" what that does this encompass? Is this a primary, secondary or tertiary amine? Is the "C_{1-6}-alkylamino" bound to the molecule

through N or carbon? When R2 and R3 form a "pyrollidinyl" "piperazinyl" "piperidinyl" "morpholinyl" or "homopiperidino" where is the point of attachment to the rest of the molecule? If "piperidinyl" is correct why is "homopiperidino" not "homopiperidinyl"? Claim 25 recites a "process for controlling a disorder or disease related to pain". What does this mean, "related to pain"? Related in what way? As in a disease that causes pain? If this was cancer pain, is this a claim to treat cancer? Claim 25 also recites a "VR1-antagonisticly effective amount" is this meant to be "antagonistically". How do we know what that is? "VR1-antagonisticly[sic] effective amount" is not appropriate language see Ex parte Dobson et. al. 165 USPQ 29.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5 & 7, 20, 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a handful of compounds that might be useful in treating pain, it does not reasonably provide enablement for the excessively protracted list of compounds and diseases claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of substituted phenyl derivatives, heterocycles, and amines bearing multiple substitutions, as well using these compounds for treating a myriad of diseases. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. In addition these compounds are claimed to be used as drugs. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist who would make the compounds. Presumably a Medical Doctor, Veterinarian or Pharm. D. would use the compounds to treat humans or animals. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. Certain TRPV1 antagonists are known to be useful in treating pain. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. Medicinal chemistry is also unpredictable **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples. As per MPEP:

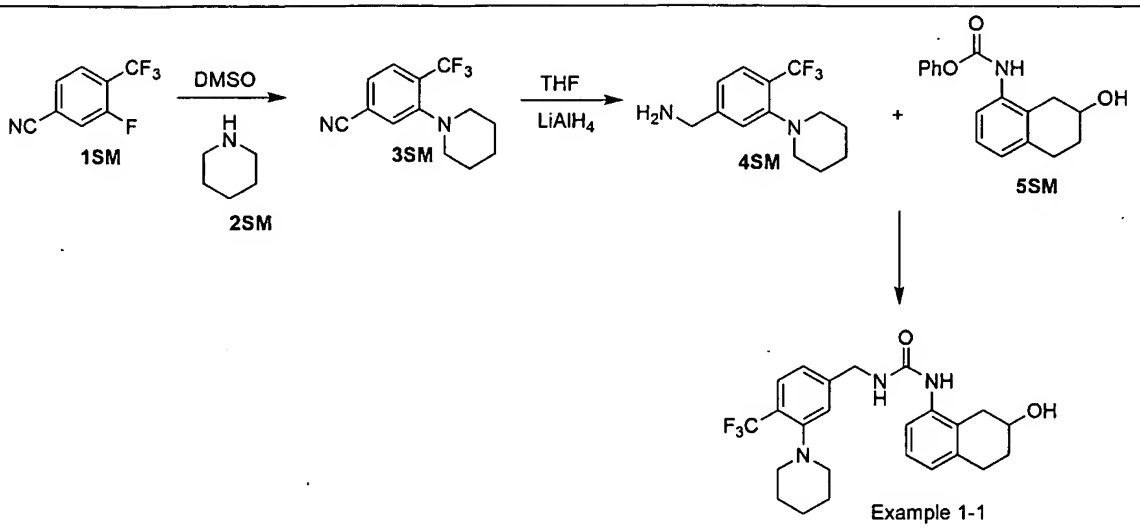
As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The specification provides us with but a single **working** example of how to prepare the compounds of the instant case. While the specification proposes several routes listed as Methods A thru G in the specification, only one of these routes is operable (Method A). Methods B is reportedly a method to make the compounds of the instant case, however it depends upon the production of the isocyanate V, however we have no way of knowing where such highly reactive compounds come from although the applicant states: "the compound (V) can be prepared by the use of known techniques or are commercially available" What known techniques? Phosgene? Which of these isocyantes are commercial? If the diamine corresponding to V is treated with phosgene such a diamine will react with at both amines resulting in either diisocyanates or polyisocyanourates and in other instances depending on where the amines are

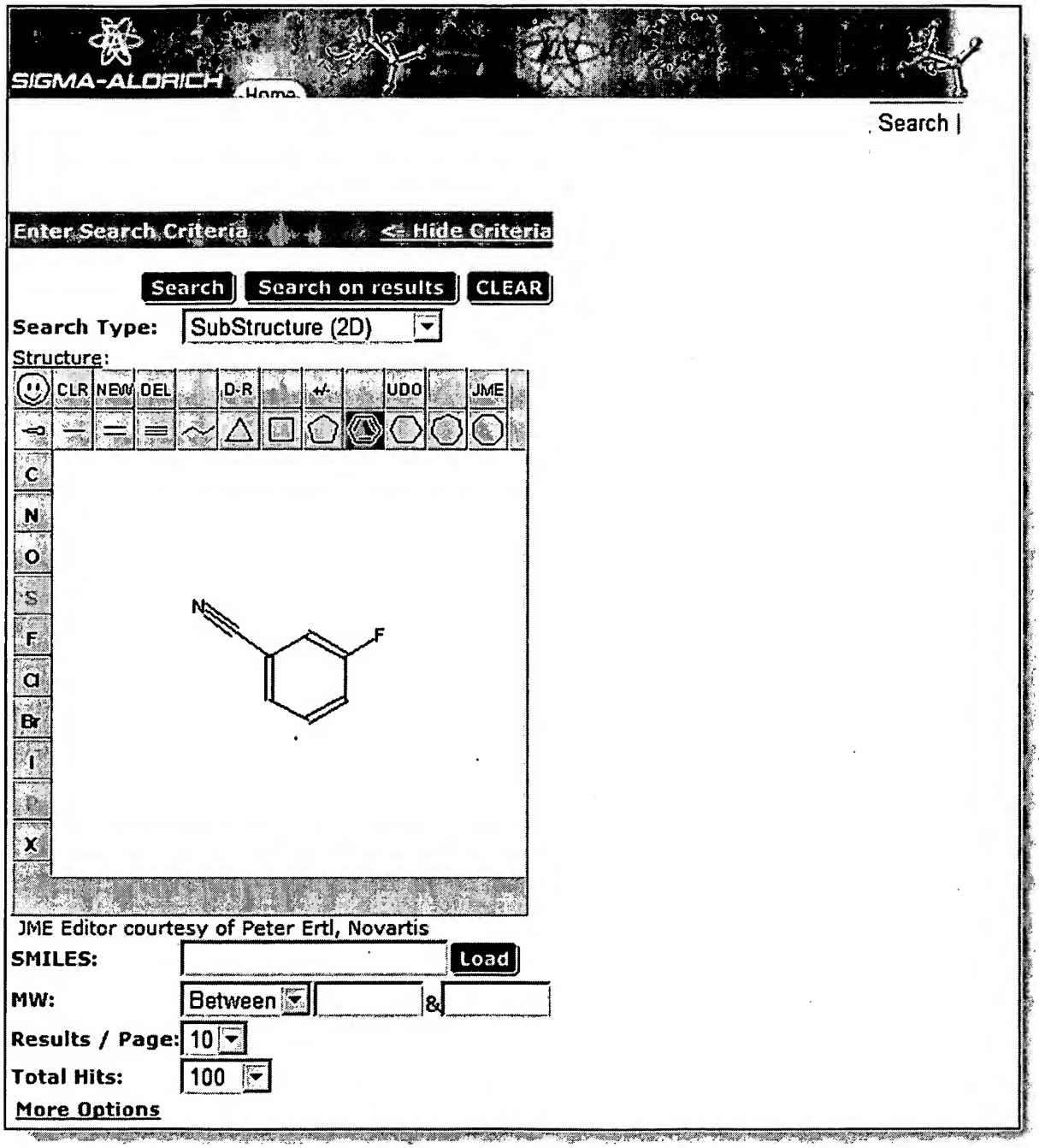
positioned cyclic ureas will be produced. Method C is even more implausible which apparently involves adding phosgene to both a diamine (IV) and the amino alcohol (II). This is a good way to make urethanes (see Wagner et. al. U. S. Patent 3,142,699) or mixtures of polyureas/polyurethanes, or other oligomers (Bachmann et. al. *Macromolecular Chemistry and Physics* **2001**, *202*, 3410-3419; Chen et. al. U.S. Patent 4,477,389). Method D **is** apparently Method B, and therefore suffers from the same limitations aforementioned. Method E seems to rely on the impossible discrimination of a chloroformate ester between two amino groups. It is well known in the art that chloroformates are some of the most reactive electrophiles and they will not discriminate between these amines. Method F is the OH protected version of Method B which suffers from the same problems as method B due to the lack of ways to make compounds such as V. It seems possible that Method G could work, although we are provided no guidance as to the source of compound X. Thus it is very clear that the only method that is operable is method A, which is of course the only working example, Example 1-1.

The synthesis of Example 1-1 is reproduced in Scheme 1:



Scheme 1. Applicant's Working Example for Preparation of the Compounds of the Instant Case.

Starting from the fluorobenzonitrile **1SM**, coupling to piperidine **2SM**, to give the N-Aryl piperidine **3SM**, followed by reduction of the nitrile to the benzyl amine **4SM**, which is subsequently coupled to the carbamate **5SM** to give Example 1-1. While Table 1, pg. 47 has 26 other examples of compounds of the instant case and we are told on pg. 46 that "in the similar manner as described in Example 1-1, compounds in example I-2 to I-28 as shown in Table 1 were synthesized". In order to prepare the compounds commensurate with the scope of the claims 1-3, 5 & 7 we require starting materials corresponding to **1SM** and **2SM** or **3SM**. A quick search of the Aldrich Chemical Company (St. Louis, MO), show that only handful of fluorobenzonitriles such as **1SM** are commercially available:

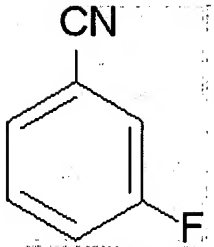


Sort By:

MW

Compound Properties	Structure	Add	Prod. #	Purity
Name: 3-Fluorobenzonitrile **IUPAC:** 3-fluorobenzonitrile **MF:** C_7H_4FN **CAS #:** 403-54-3 **MW:** 121.11	**Score:**100		235822	98%

MDL #: MFCD00001797
MP: -16 °C
BP: 182 - 183 °C
FP: 154 °C
d: 1.1330

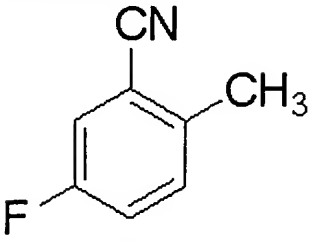


Zoom In

Name: 5-Fluoro-2-methylbenzonitrile
IUPAC: 5-fluoro-2-methylbenzonitrile
MF: C_8H_6FN
CAS #: 77532-79-7
MW: 135.14
MDL #: MFCD00042295
MP: 43 - 45 °C
FP: 175 °C

Score:90

☐ 364916 98%

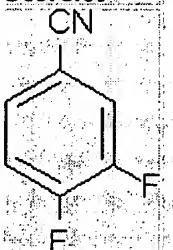


Zoom In

Name: 3,4-Difluorobenzonitrile
IUPAC: 3,4-difluorobenzonitrile
MF: $C_7H_3F_2N$
CAS #: 64248-62-0
MW: 139.10
MDL #: MFCD00011666
MP: 52 - 54 °C
FP: 157 °C

Score:89

☐ 264334 98%

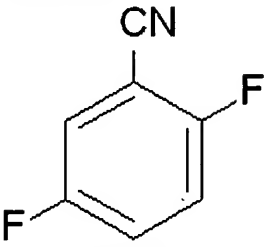


Zoom In

Name: 2,5-Difluorobenzonitrile
IUPAC: 2,5-difluorobenzonitrile
MF: $C_7H_3F_2N$
CAS #: 64248-64-2
MW: 139.10
MDL #: MFCD00001777
MP: 33 - 35 °C
FP: 172 °C

Score:87

☐ 248037 99%

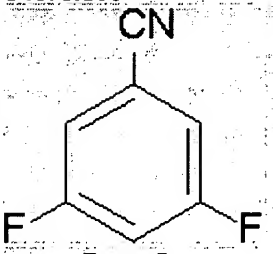


Zoom In

Name: 3,5-Difluorobenzonitrile
IUPAC: 3,5-difluorobenzonitrile
MF: $C_7H_3F_2N$
CAS #: 64248-63-1
MW: 139.10
MDL #: MFCD00010311
MP: 84 - 86 °C

Score:100

☐ 290203 99%



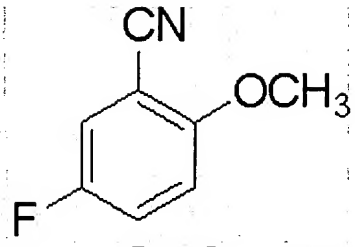
Zoom In

Name: 5-Fluoro-2-methoxybenzonitrile
IUPAC: 5-fluoro-2-methoxybenzonitrile
MF: C_8H_6FNO
CAS #: 189628-38-4

Score:63

☐ 527734 98%

MW:	151.14
MDL #:	MFCD02683503
MP:	117 - 120 °C

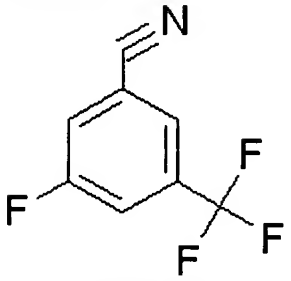


Zoom In

Name:	ALPHA,ALPHA,ALPHA,5-TETRAFLUORO-M-TOLUNITRILE
IUPAC:	3-fluoro-5-(trifluoromethyl)benzonitrile
MF:	$C_8H_3F_4N$
CAS #:	
MW:	189.11
MDL #:	MFCD00061282

Score:72

R279226

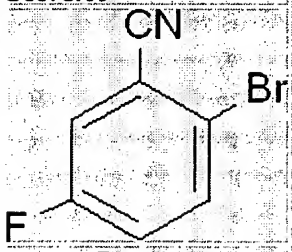


Zoom In

Name:	2-Bromo-5-fluorobenzonitrile
IUPAC:	2-bromo-5-fluorobenzonitrile
MF:	C_7H_3BrFN
CAS #:	57381-39-2
MW:	200.01
MDL #:	MFCD00142875
MP:	92 - 95 °C

Score:69

532754 97%



Zoom In

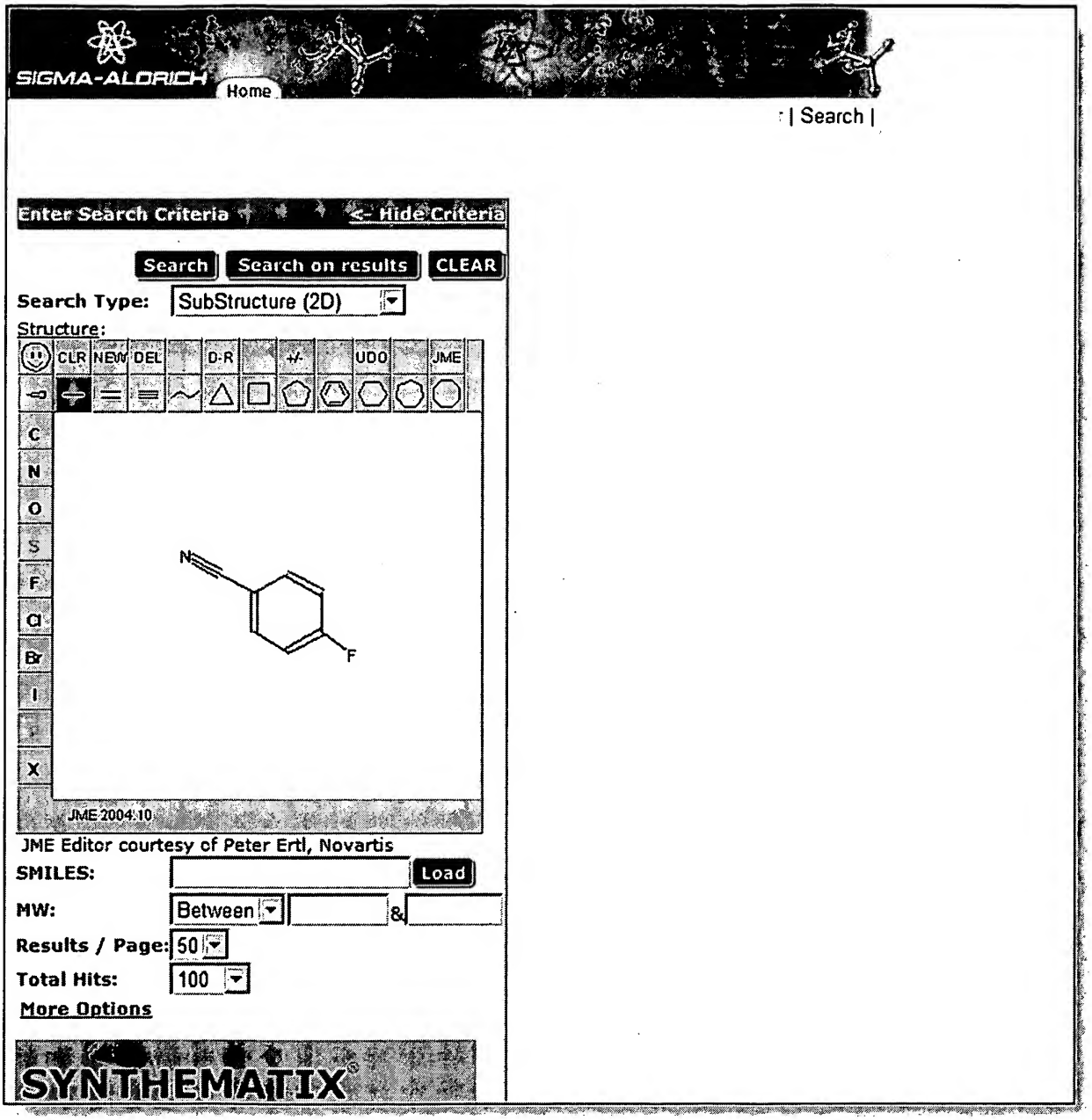
It is clear that only 8 such compounds are commercial. Of these three are difluorinated, which would likely lead to amination at both positions. It is thus very clear that the only

substituents enabled are CH_3, OMe, and Br in the very precise positions as shown above. Shockingly we cannot imagine where the trifluoromethylated compounds come from. Where can one buy or find the directions to prepare the trifluoromethylated compound **1SM** needed to practice the invention?

Moreover it would seem that these reactions require an activating group either in *o*- or *p*- positions in order for the amination to proceed (Holland, et. al. *Synthesis* **2002**, 2379-2382:

> Nucleophilic aromatic substitution reactions are widely used in synthetic methodology.[8] These reactions are enhanced when the leaving group is ortho or para to an electron withdrawing species such as formyl[9] or boronate, and in addition fluorine is a particularly good leaving group due to its substantial negative inductive effect.[10] Nijhuis and co-workers have previously reported a similar reaction where a fluorine ortho to a formyl group was replaced by a number of N-mono-substituted piperazines.[11a].

It is strange to the examiner that the conditions recited for the conversion of **1SM** and **2SM** to **3SM**, requires no base (pg. 44). Is this correct? The para analogues of **1SM** required for the synthesis of examples 5, 6, 7, 8, 10, 15, 19 are equally rare, as a simple search reveals:

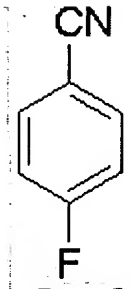


Name: 4-Fluorobenzonitrile
IUPAC: 4-fluorobenzonitrile
MF: C_7H_4FN
CAS #: 1194-02-1
MW: 121.11
MDL #: MFCD00001812
MP: 32 - 34 °C

Score: 100

☐	46680	purum, ≥98.0% (GC)
☐	139416	99%

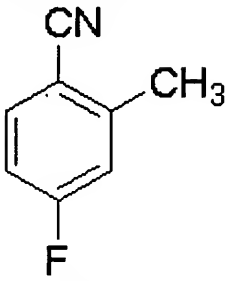
BP: 188 °C
FP: 150 °C



Zoom In

Name: 4-Fluoro-2-methylbenzonitrile
IUPAC: 4-fluoro-2-methylbenzonitrile
MF: C_8H_6FN
CAS #: 147754-12-9
MW: 135.14
MDL #: MFCD03095106
MP: 70 - 74 °C

Score:84

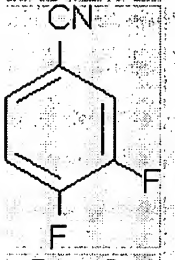


Zoom In

594660 97%

Name: 3,4-Difluorobenzonitrile
IUPAC: 3,4-difluorobenzonitrile
MF: $C_7H_3F_2N$
CAS #: 64248-62-0
MW: 139.10
MDL #: MFCD00011666
MP: 52 - 54 °C
FP: 157 °C

Score:80

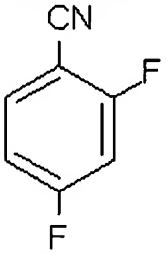


Zoom In

264334 98%

Name: 2,4-Difluorobenzonitrile
IUPAC: 2,4-difluorobenzonitrile
MF: $C_7H_3F_2N$
CAS #: 3939-09-1
MW: 139.10
MDL #: MFCD00009826
MP: 47 - 49 °C
FP: 230 °C

Score:84



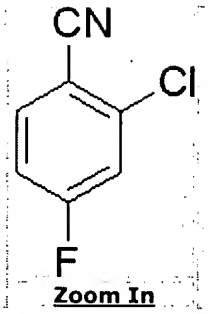
Zoom In

264326 97%

Name: 2-Chloro-4-fluorobenzonitrile
IUPAC: 2-chloro-4-fluorobenzonitrile
MF: C_7H_3ClFN
CAS #: 60702-69-4
MW: 155.56
MDL #: MFCD00042523
MP: 64 - 66 °C

Score:67

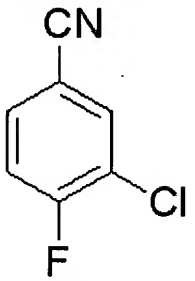
344265 99%



Zoom In

Name:	**3-Chloro-4-fluorobenzonitrile**
IUPAC:	**3-chloro-4-fluorobenzonitrile**
MF:	C_7H_3ClFN
CAS #:	117482-84-5
MW:	155.56
MDL #:	MFCD00015431
MP:	69 - 71 °C

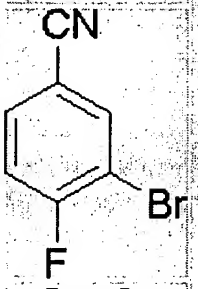
Score:64 376582 99%



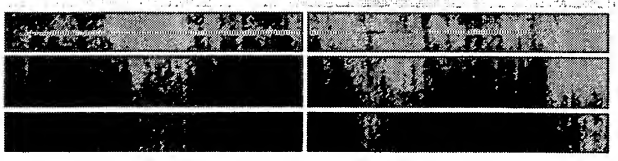
Zoom In

Name:	**3-Bromo-4-fluorobenzonitrile**
IUPAC:	**3-bromo-4-fluorobenzonitrile**
MF:	C_7H_3BrFN
CAS #:	79630-23-2
MW:	200.01
MDL #:	MFCD00055432
MP:	54 - 58 °F
FP:	230 °F

Score:63 571512 97%



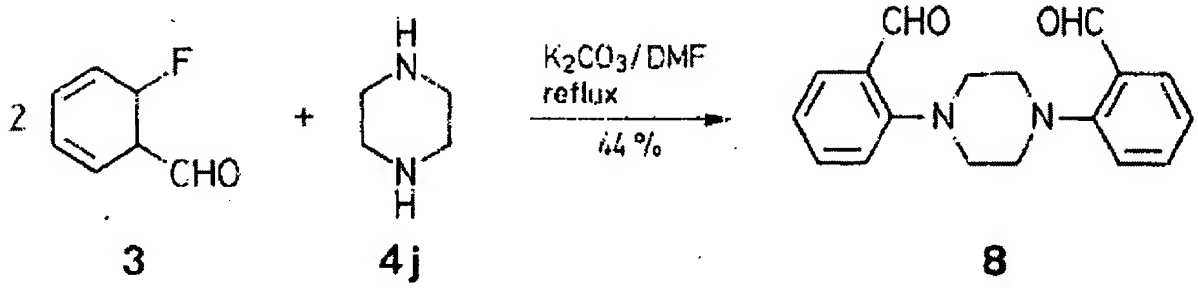
Zoom In



We can clearly see only 7 compounds that are available, two of which are difluorinated. Again where are the key trifluoromethylated compounds? In addition some of the compounds reported Example I-25 in particular is not enabled via the method of

Example I-1. It is well known that piperazines will of course undergo alkylayion at both nitrogens see Nijhuis, et. al. *Synthesis* **1987**, 641-643, where the author states:

> We have also tried to synthesize the basic skeleton **2** (R = H) in this way. Reaction of 2-fluorobenzaldehyde (**3**) with piperazine (**4j**, R = H) did not give the desired piperazinylbenzaldehyde **5j** (R = H), but rather the bis-substituted piperazine **8** in 44% yield.



3 **4j** **8**

It is also worth noting that claim 1 encompasses not only ureas derived from benzyl amines, but also anilines as well as what appears to be long alkyl chain derivatives (up to six carbons). Perhaps this was an error by the applicant, the examiner is unsure. No guidance has been provided as to how one may arrive at the amines with other alkyl chains. In regard to the anilines, the method of example 1-1 of course cannot be used to prepare anilines corresponding to **4SM** required for examples I-2, I-3, and I-4. In addition R1 can apparently be alkyl, where do the required secondary amines come from?

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard

arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how the many required staring materials of formula **1SM, 3SM, 4SM,** or the numerous substituted amines **2SM** are to be obtained. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula). Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful

conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." In addition claims 1 and 2 recite groups that are unknown to the examiner (1,3,2-dithiazocane 1,3,2-dithiazepane) or heretofore theoretical molecules (1,3,2-dioxazetidine and 1,3,2-dithiazetidine) Figure 1.

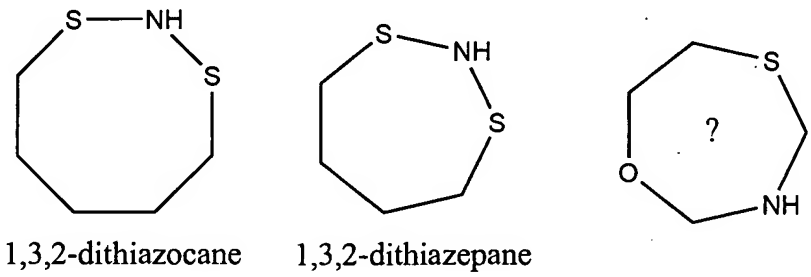


Figure 1. Possibilities for R2 and R3?

While it is very clear that no one can make the scope of the invention. It is also very clear that no one can use the full scope of the invention. The applicant has given the public little guidance as to what these compounds do in the physiological sense. The sole statement we are given: "For practical reasons, the compounds are grouped in four classes of activity as follows: IC50- A < or = 0.11μM B < or = 0.5μM C < or = ~ 1μM < D The compounds of the present invention also show excellent selectivity, and strong activity in other assays 2-5 described above." A mention of "selectivity" is given. Is this a reference to activity at the putative purinergic receptor? From an examination of the

trends given in Table 1 it is clear that a very minor change in the structure of the antagonist results in dramatic changes in activity. For example a bioisosteric replacement of the 4-methylene group of piperidine (Example 1-1) with an NH as in piperazine Example I-25 results in compounds with a at least a 10 fold decrease in activity. The compounds of broad claims of 1-3, 5-7, 25, 27 would likely not work as antagonists. It would appear the benzyl ring should bear a lipophilic group like trifluoromethyl or iPr. Certainly we cannot expect compounds containing sulfur or various optional substituents to function as antagonists even if they could be prepared. The pharmacology of TRPV1 is complex, with the receptor expressed both centrally and peripherally. It is worth pointing out that while capsaicin is an effective tool as agonist when doing high-throughput pharmacology, it is not the endogenous ligand for TRPV1. Protons and heat and possibly a few lipids are thus far the only known endogenous ligands for this receptor. Is this antagonism competitive or non-competitive? We do not know. While these compounds are reported to have "strong activity" the language employed in the specification (not past tense) suggests that these experiments were either being performed or were not performed at the time of filing. Regardless for pain treatment we have only rat DRG data to rely upon and as pointed out by Szallasi et. al. *TRENDS in Molecular Medicine* **2006**, *12*, 545-554:

> "Given the species-related differences in both the neurochemistry of capsaicin-sensitive neurons [2] and the pharmacological properties of TRPV1 [99], one should exercise utmost caution when extrapolating results obtained in rodents to humans."

So while potentially useful for treating pain in some rodents, we cannot believe that these compounds would be useful for treating pain in humans. The species variation of the receptor in mammals is quite significant as has been summarized by Ohta et. al. *Biochemical Pharmacology* **2005**, *71*, 173-187, pg. 174 column 1:

> "There are some notable species differences in the compound sensitivities of these channels. For instance, capsaicin has an agonistic action in most mammalian orthologues except for rabbit TRPV1 [12]. Indeed, rabbit dorsal root ganglion (DRG) neurons are resistant to the acute toxicity of capsaicin [18] and have no resiniferatoxin-binding site [19]. Furthermore, human [10] and guinea-pig TRPV1 [11] have little sensitivity to PPAHV, while rat [10,20], mouse [13] and dog TRPV1 [14] are significantly sensitive to PPAHV. RTX is more potent than olvanil in guinea-pig TRPV1 [11], but it is the opposite in other species [13–15,20]. Capsazepine, a TRPV1 antagonist, inhibits the response to acidic pH in human [10] and guinea-pig TRPV1 [11], but not in rat [10] and mouse TRPV1 [13]. For studying pain research in vivo, a number of reports have been published using rodent models. However, because of the inability of capsazepine to inhibit all modes of rat and mouse TRPV1 activation, it is suggested that use of a rodent model for studying TRPV1 antagonists may not accurately reflect the role of TRPV1 in human pathophysiology [13]."

It is abundantly clear that rabbits will not benefit from a molecule that antagonizes the effects of capsaicin since they lack sensitivity to capsaicin. In addition, the animal

models chosen will not accurately predict the use of these compounds in humans. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make or use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

5. Claims 19, 21, 22, 24, 25, 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims drawn toward inflammatory diseases and urological disorders are not enabled. The aforementioned discussion of the species differences in the TRPV1 receptor applies here, *vide supra*. Apparently some interest in TRPV1 antagonists as COPD and asthma treatments has revealed promising results as evidenced by the most recent study available to the examiner (Skogvall, S. et. al. *Pulmonary Pharmacology and Therapeutics* **2007**, 20, 273-280, pg. 279 column 2, to p.g 280) however the author expresses the view that the results with the canonical TRPV1 antagonist in tissue must be translated to in-vivo effects:

> "Hence, a novel principle such as the present capsazepinoids that reliably inhibit contractile effects **may be a useful** addition to the presently available drugs to treat diseases such as asthma and COPD. Since COPD and to a significant extent asthma may be considered small airways diseases [22,23] it is of particular interest that the present compounds exhibit efficacy in human small bronchi. Indeed, since previous work involving animal studies [4,16,24] has failed to identify the general bronchorelaxing properties of capsazepine the present discovery apparently required the use of human bronchial preparations as a primary study approach.
> In conclusion, capsazepine and some closely related analogues have been found to inhibit human small airway responsiveness to contractile mediators. If potency can be further increased **and the results translated to in vivo,** compounds representing this novel class of bronchorelaxants might become useful in the treatment of patients suffering from asthma and COPD. The present results thus stress the need of structure–activity relationship studies for this class of compounds as well as further investigations into their mechanism of action." Emphasis added.

In the instant case, these are very different compounds that were not tested in tissues (other than Chinese Hampster Ovary cells). With respect to overactive bladder, we must come to the conclusion that this area is highly unpredictable as stated by Szallasi et. al. (ibid.):

"Despite the mounting evidence that suggests a therapeutic value for TRPV1 antagonists in the symptomatic treatment of interstitial cystitis (IC), a word of caution seems reasonable at the moment. Resiniferatoxin (RTX) has been assayed intravesically in IC patients with the expectation that TRPV1 desensitization should be able to decrease both pain and urinary frequency. The results of the two available placebo-controlled clinical trials are conflicting: one suggests clinical utility [73], whereas the other does not demonstrate any advantage from TRPV1 desensitization [74]. Patients with neurogenic and non-neurogenic forms of detrusor overactivity, in contrast with IC patients, responded positively to intravesical RTX.....**Therefore, the effect of a strong TRPV1 antagonist on urinary frequency and incontinence of patients with detrusor overactivity is still unpredictable**." Emphasis added.

As per the MPEP 2164.04:

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection.
The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then

> drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-3, 5, 7, 19-26 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 8-20 of copending Application No. 10/513,848. This

is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The method claims from which they depend are essentially the same.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

7. Claims 1-3, 5, 7, 19-26 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 6-22 of copending Application No. 10/575,027. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

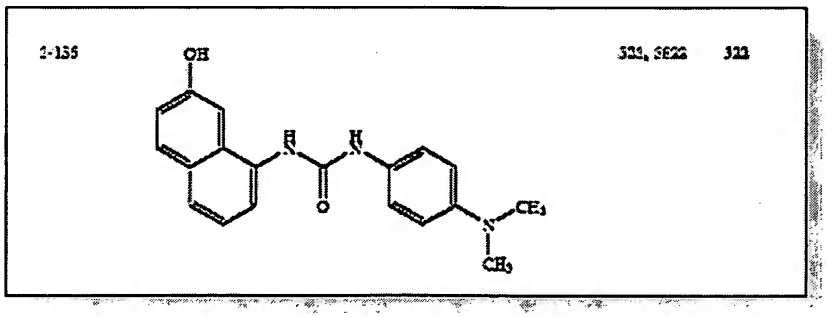
The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The method claims from which they depend are essentially the same.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

8. Claims 1-3, 5, 7, 19-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/485,481 in view of Walpole, et. al. *J. Med. Chem.* **1994**, *37*, 1942-1954. This is a provisional obviousness-type double patenting rejection. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) **Determining the scope and contents of the prior art:** The '481 application claims compounds such as Example I-136:



among others (including morpholinyl derivatives). Walpole et. al. teach the synthesis of TRPV1 antagonist that are bicylcic 6-membered saturated benzofused ring compounds, such as compounds **7a** thru **8b**.

B) Ascertaining the differences between the prior art and the claims at issue: The only difference in the compounds of the instant invention and those of the '481 application is the presence of four hydrogen atoms in the former.

C) Resolving the level of ordinary skill in the pertinent art: The level of ordinary skill in the art is extremely high. Typical researchers have a Ph.D. in organic chemistry, post-doctoral training and many years of experience in diverse fields.

D) Considering objective evidence present in the application indicating obviousness or nonobviousness. In the field of TRPV-1 receptor modulators (the instant case), such modifications are well known to lead to increased receptor binding. Walpole has shown that bicylcic 6-membered saturated benzofused ring compounds possess properties associated with antagonism. Thus it is submitted that the tetrahydro -naphthalene compounds of the instant case are obvious variants of the naphthalene of the '481 application based on the teachings of Walpole et. al.. The artisan of ordinary skill would be motivated to make the change in order to increase the lipophilicity of the compound with the expectation that potency would be maintained.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell, Ph.D. whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.